Reduction in Severe Hypoglycemia With Long-Term Continuous Subcutaneous Insulin Infusion in Type I Diabetes

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OBJECTIVE — To compare the incidence of severe hypoglycemia in patients crossed over from multiple daily injections (MDIs) of insulin to continuous subcutaneous insulin infusion (CSII).

RESEARCH DESIGN AND METHODS — From a population of 255 patients using CSII, all patients who met the following selection criteria were included in the present study: *1*) a minimum of 12 months on intensive therapy with MDIs before switching to CSII, and 2) a minimum of 12 months on CSII after crossover. Glycemic control and adverse event rates for the 1-year MDI control period were compared with those for the CSII therapy period.

RESULTS — The incidence of severe hypoglycemia during MDI therapy declined from 138 to 22 events per 100 patient-years during the 1st year of CSII ($P < 0.0001$) and remained significantly lower in years 2, 3, and 4 on CSII (26, 39, and 36, respectively). HbA_{1c} levels did not change significantly between the MDI phase and any year on CSII. However, in the subgroup of patients who had pre-CSII HbA_{1c} levels of ≥8.0%, the change to CSII was associated with a significant reduction in HbA_{1c} from baseline to year 1 (8.9 ± 0.8 vs. 8.1 ± 1.0%, $P = 0.0004$). The difference in diabetic ketoacidosis rates between the MDI year (14.6 events per 100 patient-years) and the CSII period (7.2 events per 100 patient-years) was not statistically significant.

CONCLUSIONS — CSII therapy was associated with a marked and sustained reduction in the rate of severe hypoglycemia without adversely affecting the level of glycemic control attained during MDI therapy. The more reproducible and flexible insulin delivery afforded by CSII was considered to be the major factor contributing to the improvement in severe hypoglycemia rates.

Intensive treatment of diabetes, with the goal of near-normalization of blood glucose levels, has been shown to delay and reduce long-term complications of type I diabetes (1–3). In the Diabetes Control and Complications Trial (DCCT), however, improved glycemic control through intensive therapy was accompanied by a threefold higher rate of severe hypoglycemia relative to that observed in conventionally treated patients (3). This increase was observed in both patients using predominantly continuous subcutaneous insulin infusion (CSII) and those using predominantly multiple daily injection (MDI) therapy (4).

CSII has been shown to provide more predictable insulin absorption than MDIs of modified insulin (5–9). It permits programmed changes in basal insulin delivery to compensate for periods of high hypoglycemia risk (such as those occurring nocturnally) or the increased insulin need that accompanies the dawn phenomenon (10,11). In other studies of long-term CSII use, sustained improvement in glycemic control has been accompanied by reductions in the incidence of severe hypoglycemia (12–17).

The objective of this prospective study was to investigate the effects of CSII-based intensive therapy in patients who had experienced severe hypoglycemia and/or had not achieved desirable levels of glycemic control after at least 1 year on MDI therapy.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS — From a population of 255 patients using CSII, all patients who met the following selection criteria were included in the present study: *1*) minimum of 12 months on intensive therapy with MDIs before crossover; and 2) minimum of 12 months on CSII-based intensive therapy after crossover. Criteria for switching a patient from MDI to CSII therapy included: *1*) suboptimal glycemic control as shown by fluctuating blood glucose levels thought to be associated with poor response to intermediate-acting insulin; 2) HbA_{1c} >8.0%; 3) a history of recurrent severe hypoglycemia (defined as one or more episodes per year of hypoglycemia requiring the assistance of another person); or 4) hypoglycemic unawareness.

The intensive therapy program during both study phases was identical in all respects except mode of insulin delivery:

1. Self-monitoring and recording of blood glucose before each meal, at bedtime, once a week at 3:00 A.M., and at other times, as needed, using a memory meter.
2. Administration of algorithm-based insulin dose adjustments and supplemental insulin, as needed, to achieve target blood glucose levels. Patients calculated premeal insulin bolus doses by means of carbohydrate counting and individualized carbohydrate/insulin ratios; supplemental doses were calculated using

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CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; MDI, multiple daily injection.

Table 1—*Key outcomes by study year*

	MDI	CSII			
		Year 1	Year 2	Year 3	Year 4
HbA_{1c} (%)	7.7 ± 1.5 (55)	7.4 ± 1.2 (55)	7.7 ± 1.7 (41)	7.4 ± 1.7 (26)	7.4 ± 1.2 (20)
Severe hypoglycemia (events per 100 patient-years)	138 (55)	22 (55)*	26 (50)‡	39 (33)*	36 (25)‡
Weight (kg)	67.4 ± 14.4 (55)	68.1 ± 14.1 (55)§	69.7 ± 15.2 (41)	70.0 ± 14.6 (25)§	68.0 ± 15.2 (21)
Total insulin dose (U/day)	42.9 ± 17.9 (52)	36.4 ± 12.1 (54)*	39.6 ± 14.4 (38)‡	37.7 ± 13.1 (25)	37.8 ± 14.2 (19)

Data are means ± SD (*n*). For MDI, the last HbA_{1c} level recorded before CSII initiation was used as the baseline value. This table does not reflect continuation of CSII pump therapy. For inclusion in the study, patients were required to have worn the pump for a minimum of 12 months, and some patients wore it for as long as 4 years. *P* values for severe hypoglycemia were calculated using the sign test; those for weight and total insulin dose were calculated using Student's *t* test. Significance level of difference from baseline: *$P < 0.0001$; †$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$.

each patient's individualized insulin sensitivity factor and target blood glucose level (18).

3. Individually established target blood glucose ranges, based on each patient's clinical history. In patients with no history of severe hypoglycemia, the premeal target range was 70–150 mg/dl (3.9–8.3 mmol/l). In patients with reduced hypoglycemic awareness, the premeal target range was 80–160 mg/dl (4.4–8.9 mmol/l); if recurrent severe hypoglycemia was present, a higher target range was used.
4. Quarterly routine visits and 24-h telephone support. During the initiation phase of either therapy and whenever they were having difficulty controlling their blood glucose levels, patients were requested to fax their blood glucose record sheet twice a week to the health care team for review and telephone consultation. Patients on either regimen were asked to telephone the health care team and to record a note on their blood glucose record sheet whenever they experienced an episode of severe hypoglycemia.
5. Hypoglycemia prevention and treatment. Patients were instructed to treat hypoglycemia with 10 g of glucose, to recheck their blood glucose in 20 min to ensure response, and to adjust their insulin dose in response to an unexplained below-target blood glucose level.
6. Comprehensive diabetes education. All patients participated in a self-care education program at initiation of MDI; self-care practices were reviewed when patients crossed over to CSII.

All patients were started on CSII therapy as inpatients in a diabetes unit. A programmable, external insulin pump (model 504 or 506, MiniMed, Sylmar, CA) was used to deliver phosphate-buffered regular insulin (Velosulin, Novo-Nordisk, Princeton, NJ), with the initial dosage calculated as 75% of the prepump total daily insulin dose. Of the insulin dose, 50% was given as a single basal rate and the remaining 50% in three equal premeal boluses for three meals of equal carbohydrate content, with no bedtime snack. Additional basal rates were instituted as needed based on routine blood glucose monitoring.

Data were gathered prospectively during both the MDI and CSII phases of the study. HbA_{1c} and body weight were measured and recorded at each routine visit. Values for total daily insulin dose, frequency of self-monitoring, severe hypoglycemia incidence, and diabetic ketoacidosis (DKA) incidence were obtained at each visit from the patient's personal diabetes log sheet. Patients were also asked at each visit to report any unrecorded episodes of hypoglycemia that required the assistance of another person.

Statistical analysis

The last HbA_{1c}, body weight, and total daily insulin dose values recorded when the patient was using MDIs before crossover to CSII were used as the baseline values. Single-sample Student's *t* tests were used to evaluate the significance of any change from baseline. The number of severe hypoglycemia and DKA episodes during the MDI year and during each year of CSII were calculated for each patient. To accommodate the positive skew present in both hypoglycemia and DKA data, the sign test was used to evaluate changes in event rates from the MDI to the CSII period.

RESULTS — Fifty-five patients (35 women and 20 men) were included in the study. At baseline, their age was 39.2 ± 12.9 (mean ± SD) years, and duration of diabetes was 22.2 ± 9.7 years. The patients used CSII for a mean of 3.1 years; 170.4 patient-years of CSII experience are included in the analysis.

Glycemic control did not change significantly from baseline (MDI) during any year of CSII therapy (Table 1). However, a significant improvement in mean HbA_{1c} from baseline to year 1 was seen with patients who had unacceptable glycemic control at baseline, defined as an $HbA_{1c} \geq 8.0\%$ (8.9 ± 0.8% vs. 8.1 ± 1.0%, $P = 0.0004$). In contrast, the 30 patients who had better glycemic control at baseline, defined as an $HbA_{1c} < 8.0\%$, showed no difference in control from baseline to year 1 (6.7 ± 1.1 vs. 6.8 ± 1.2%, NS).

The rate of severe hypoglycemia declined significantly with CSII use. While patients experienced a total of 76 severe hypoglycemic events during the 1-year MDI period, only 12 severe episodes were observed during the 1st year on CSII therapy. Severe hypoglycemia rates declined from 138 to 22 events per 100 patient-years from the baseline MDI period to year 1 of CSII and remained significantly lower in years 2, 3, and 4 on CSII (26, 39, and 36 events per 100 patient-years, respectively [Table 1 and Fig. 1]). In the 25 patients with $HbA_{1c} \geq 8.0\%$, the rate of severe hypoglycemia declined significantly, from 84 events per 100 patient-years at baseline to 8 events in year 1 ($P < 0.0001$). The 30 patients with baseline $HbA_{1c} < 8.0\%$ also experi-

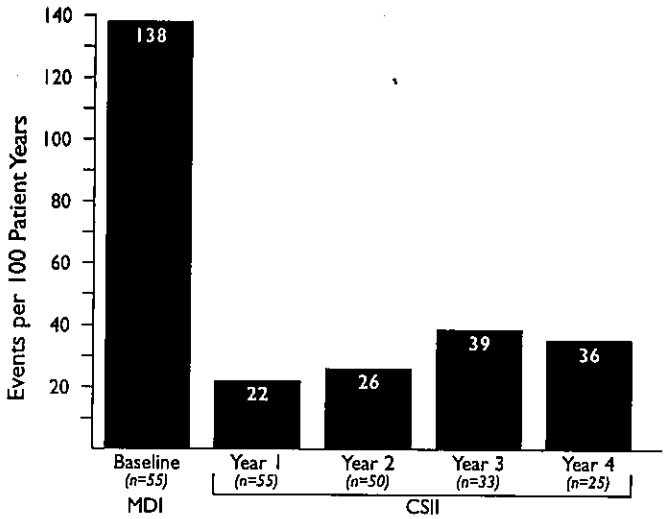

Figure 1—*Severe hypoglycemia (events per 100 patient-years) at baseline (MDI) and by year on CSII. P values, calculated using the sign test, are as follows: year 1, P = 0.0001; year 2, P = 0.0036; year 3, P = 0.0001; year 4, P = 0.0032.*

enced a decline, from 183 to 33 severe hypoglycemic events per 100 patient-years ($P = 0.0005$).

DKA rates were not significantly different between the MDI and the CSII phases (14.6 vs. 7.2 events per 100 patient-years, respectively). Although weight gain was not significantly different from baseline to years 1 or 4, a small (2.3–2.6 kg), yet significant, weight gain was observed at years 2 and 3 (Table 1).

The mean total daily insulin dose 1 year after initiation of CSII (36.4 ± 12.1 U/day) was 15% lower than the pre-CSII dose (42.9 ± 17.9 U/day) and remained lower over the 4-year observation period (Table 1). The majority of patients (31 patients, 56%) used two to three basal rates, 14 (25%) patients used a single rate, 8 patients (15%) used four rates, 1 (2%) patient used five rates, and 1 (2%) patient used six rates.

CONCLUSIONS— In the present study, use of an insulin pump was associated with a marked and sustained decrease in the incidence of severe hypoglycemia from that seen during the control period of MDI-based therapy. This decrease in severe hypoglycemia was accompanied by a sustained level of good glycemic control (HbA_{1c} <8.0%) in those who had achieved it with MDI therapy and by an improvement in glycemic control in those patients who had an HbA_{1c} ≥8.0% with MDI. Mean HbA_{1c} levels in this study were similar to those seen in the intensive treatment group of the DCCT (3).

The relatively high rate of severe hypoglycemia observed during the MDI year (138 events per 100 patient-years) may be attributed to the inclusion of patients with a history of severe hypoglycemia and/or hypoglycemic unawareness, the latter group having been shown to have a sixfold higher incidence of severe hypoglycemia than patients without impaired awareness (19). In contrast, the DCCT, after the feasibility phase, excluded patients who were at high risk for severe hypoglycemia, defined as those who had experienced, in the previous 2 years, more than two episodes of seizure or coma or more than one episode of severe neurological impairment without warning symptoms of hypoglycemia (20). Gold et al. (19) estimated the overall incidence of severe hypoglycemia in insulin-treated patients with and without hypoglycemic unawareness at 160 events per 100 patient-years, a higher rate than that observed during the MDI phase of the present study.

Pharmacokinetic factors probably contributed to the relatively low rate of severe hypoglycemia with CSII in this study. Absorption of regular insulin from the subcutaneous tissue after CSII administration has been shown to vary by <2.8% from the administered 24-h dose, providing a high level of day-to-day reproducibility in insulin availability and a minimum of unexpected fluctuations in glycemic control (8). In contrast, injected insulin preparations show highly variable absorption, ranging from 10 to 52% of the injected daily dose (8). Thus, patients may have attained more stable blood glucose levels with CSII than they were able to achieve with MDI, which would have reduced their risk for hypoglycemia. CSII also gave patients the capability to program alternate basal rates during periods of reduced insulin need and to give insulin boluses in increments of tenths of a unit. Both of these features may have helped them to avoid hypoglycemia and/or correct it before it became severe.

In this study, the total daily insulin dose with CSII was 7–15% lower than that used during the MDI phase of the study. These small reductions in bolus and basal insulin requirements may have resulted in lower plasma insulin levels in the late postprandial period and, in turn, less tendency for preprandial hypoglycemia.

Patient education at the time of CSII initiation might have been expected to positively influence study outcomes, particularly during the 1st year the patient was using CSII. All participants had received comprehensive training in intensive diabetes management before starting MDI therapy and were given refresher training at the time of pump initiation. However, because there was no trend toward deterioration in either HbA_{1c} levels or severe hypoglycemia rates over the years on CSII, it is unlikely that patient education at CSII initiation was the major factor in the improvement observed.

In conclusion, in this study, patients receiving long-term CSII therapy maintained an excellent level of glycemic control and achieved a significant reduction in the rate of severe hypoglycemia relative to the control period of intensive management with MDI therapy. As a mode of insulin delivery in intensive diabetes therapy, CSII can be used with confidence and success in the private practice setting.

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